PROTECTIVE EFFECT OF ZINC OXIDE NANOPARTICLES ON OXIDATIVE STRESS IN EXPERIMENTAL - INDUCED DIABETES IN RATS

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Abstract:

The use of nanoparticles in medicine is an attractive proposition. In the present study, the protective effect of zinc oxide nanoparticles (ZnONPs), on oxidative stress in experimental - induced diabetes in rats were evaluated. One hundred and sixty male albino rats with weight 130 ± 30 and age 12-16 weeks were used. Animals were grouped as follows: control; did not receive any type of treatment , control positive received single daily oral dose of 5 mg/kg ZnONPs in suspension, diabetic rats; received a single intra peritoneal dose of streptozotocin (50 mg/kg), diabetic + insulin; received a single daily subcutaneous dose of insulin (2U/kg) , diabetic + ZnONPs I, received single daily oral dose of 5mg/kg ZnONPs in suspension, diabetic + ZnONPs II, received single daily oral dose of 10mg/kg ZnONPs in suspension , diabetic+ ZnONPs + insulin I; received single daily oral dose of 5mg/kg ZnONPs in suspension and a single daily subcutaneous dose of insulin (2U/kg) and diabetic+ ZnONPs + insulin II; received single daily oral dose of 10mg/kg ZnONPs in suspension and a single daily subcutaneous dose of insulin (2U/kg) . The blood glucose , serum insulin, malondialdehyd (MDA) and serum nitric oxide (NO) levels were determined after 15 and 30 days of ZnONPs and/ or insulin treatment. The results indicated that the blood glucose, serum insulin, MDA and NO levels were increased while serum insulin levels were decreased in diabetic rats, while they are significantly modified in rats that administrated

ZnONPs and/or insulin in a dose dependent. In conclusion, zinc oxide nanoparticles act as potent antidiabetic through decreasing of blood glucose and increasing of serum insulin as well inhibition of lipid and protein free radicals.

Key words: ZnONPs, insulin, MDA, NO

1. Introduction

Diabetes mellitus, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. High blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) (Wild et al., 2004). A large number of people suffer from diabetes all over the world (Lin and Sun , 2010). These patients would require the development of several medications with multiple modes of actions. Many researches demonstrated the role of metals in glucose metabolism and the association of their deficiency with diabetes as Vanadium (Thompson, et al., 2009), chromium (Wang and Cefalu , 2010) magnesium (Wells, 2008), and zinc (Chausmer, 1998) have been reported to play a role in blood sugar maintenance and have been included in diabetes therapy. Zinc, an essential metal, is an activator for more than three hundred enzymes in the body (Haase et al., 2008), and plays a key role in different metabolic pathways including glucose metabolism. Zinc promotes hepatic glycogenesis through its actions on the insulin pathways and thus improves glucose utilization (Jansen et al., 2009). Zinc is also known to keep the structure of insulin (Sun et al., 2009) and has a role in insulin biosynthesis, storage and secretion (Chausmer, 1998).There are several zinc transporters in pancreatic β-cells (Smidt et al., 2009); like zinc transporter 8 which has a potent role in insulin secretion (Rungby, 2010). In addition, zinc could improve insulin signaling by several mechanisms, including increased insulin receptor phosphorylation, enhancing PI3K activity and inhibition of glycogen synthase kinase-3 (Jansen et al., 2009). Zinc deficiency is positively correlated with

diabetes and may also affect the progress of Type 2 diabetes (Chausmer , 1998). Decreased zinc in the pancreas may reduce the ability of the islet β-cells to produce and secrete insulin (Meyer and Spence , 2009). Furthermore, knowing zinc's antioxidant role (Chausmer , 1998) ,reduced zinc may exacerbate the oxidative stress-mediated complications of diabetes. Thus, there exists a complex inter-relationship between zinc, diabetes and diabetic complications. Developing a zinc-based agent for treatment of both Type 1 and Type 2 diabetes and associated complications thus becomes an attractive proposition. The beneficial role of zinc in diabetes has been implicated by studies of the zinc supplies in diabetic rats (Ukperoro et al., 2010). Alkaladi et al., (2014) reported the antidiabetic effects of ZnONPs through induction of insulin, IR and glucose metabolizing enzymes gene expression. In the same line Umrani and Paknikar (2014) proved the ability of ZnONPs for controlling of blood glucose in diabetic rats, these are only two studies that monitored the effect of ZnONPS on diabetic rats therefor this work was designed to investigate the ability of ZnONPs to modulates blood glucose, MDA ,NO and insulin levels in the STZ-diabetic rats.

2. MATERIAL AND METHODS

2.1. Experimental animals: One hundred and sixty white male albino rats, 12-16 weeks old and average body weight 130 ± 30 gm were used in the experimental investigation of this study. Rats were obtained from laboratory animals research center, Faculty of Vet. Medicine Zagazig university. Egypt.Animals were housed in separate metal cages, fresh and clean drinking water was supplied *ad-libitum* through specific nipple. Rats were kept at constant environmental and nutritional conditions during the course of the experiment. Cleaning and changing water and food was done for all animals twice daily. The animals were left 7 days for acclimatization before the beginning of the experiment. The animals were fed on constant ration through the course of the experiment in the

form of concentrated diet composed of carbohydrate 58%,protein 21%,lipid 3.4%, cellulose 2.6%,minerals 1.49% calcium 0.9% phosphorus 0.59% and moisture12%.

2.2. Zinc Oxide Nanoparticles (ZnONPs) ZnONPs was obtained in the form of dispersion (Sigma-Aldrich, Steinheim, Germany). of the following properties, concentration 50 wt.% in H_2O, the average nanoparticle size <35 nm, the particle size distribution (hydrodynamic diameter) <100 nm using dynamic light scattering (DLS) technique, pH 7±0.1(for aqueous systems) and density 1.7 g/mL±0.1 g/mL at 25 °C

2.3. Diabetes Induction: The experimental induction of diabetes in male rats was induced by a single intraperetinoel (i.p) injected dose of 50 mg /kg body wt. of streptozotocin (STZ) (Sigma Chemical Co. P.O. St. Low is, U.S.A.) freshly dissolved in citrate buffer, PH 4.5. After STZ injection the animals were allowed to drink glucose solution (5%) w/v overnight to avoid hypoglycemia which might be induced by streptozotocin (STZ). Control rats (n= 40) were received an equivalent amounts of vehicle (citrate buffer) alone .A week later, STZ–treated rats were fasted for 12 hours, and blood samples were collected from the orbital venous sinus for blood glucose determination. Rats in diabetic group with blood glucose levels higher than 250 mg /dl were considered diabetic and included for further studies (Ramanathan et al., 1999).

2.4. Animal grouping: After four weeks of diabetes induction the diabetic rats were randomly sub-divided into seven groups, 20 animals in each, placed in individual cages and classified as follow:-Group I (control non-treated group): Rats were received no drugs, served as control non-treated for all experimental groups. Group II (control positive ZnONPs treated group) Rats were received ZnONPs (5 mg / kg body weight oral daily) served as positive control ZnONPs for all experimental groups. Group III (diabetic non-treated group): Rats were received no drugs and served as STZ-induced diabetic groups. Group IV (diabetic insulin treated group): Rats were injected with 2U/kg insulin S/C daily

for one month. (Izbeki *et al.,* 2008) Group V (diabetic ZnONPs treated group I): Rats were received 5 mg /kg bwt ZnONPs orally once daily for one month (Umrani and Paknikar , 2014). Group VI (diabetic ZnONPs treated group II): Rats were received 10 mg /kg bwt ZnONPs orally once daily for one month (Umrani and Paknikar, 2014).Group VII (diabetic ZnONPs with insulin treated group I): Rats were received 5 mg /kgbwt ZnONPs orally once daily for one month (Umrani and Paknikar , 2014).and injected with insulin at dose of 2 U/ Kg subcutaneously (Izbeki et al., 2008). Group VIII (diabetic ZnONPs with insulin treated group II): Rats were received 10 mg /kg bwt ZnONPs orally once daily for one month (Umrani and Paknikar , 2014). and injected with insulin at dose of 2 U/ Kg subcutaneously (Izbeki et al., 2008). At the end of experiment rats were anesthetized, blood samples were collected and used for sepration of serum that used for determination of blood glucose, serum insulin, MDA and NO.

2.5. *Biochemical investigations*

Blood glucose (mg/dL) was estimated by glucose oxidase method using the kit supplied by SPINREACT (Sant Esteva de Bas, Girona, Spain) according to Tietz, (1995), we measured blood glucose in all experimental animals before the beginning of the experimental procedures, after streptozotocin injection. For targeted-induced diabetic animals; blood glucose was routinely measured until diabetes was detected (animals with blood glucose >250 mg/dL are indicted as diabetics). After that, blood glucose was monitored in all experimental animals, and results were obtained at the end of the experimental period. Serum insulin level was estimated using a rat insulin elisa kit (Catalog No. ezrmi-13kelisa, EMD Millipore, Billerica, MA, USA). Serum nitric oxide was determined according to the method described by Montgomery and Dymock , (1961) using kit that supplied by Biodignostic (Catalog No. TA2533, Egypt) following the manufacturer instructions and Serum lipid peroxidation (L-MDA) was

colormetrically determined according to the method adapted by (Ohkawa *et al.,* 1979).

2.6. Statistical analysis: Data analysis was expressed as mean ± S.E. and analyzed for statistical significance by one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons, using SPSS program for Windows version 15.0 (SPSS Inc., Chicago, USA). Values were considered statistically significant at *P*<0.05 correlations between the measured variables were assessed by linear regression analysis by the least squares method.

3. Results

The blood glucose, serum MDA and NO were significantly increased but serum insulin levels were significantly decreased in diabetic rats as compared with the other groups. When the diabetic rats treated with ZnONPs in doses 5 and 10 mg/kg b.w. for 30 days either alone or with insulin, blood glucose, serum MDA and NO levels were significantly decreased and serum insulin levels were increased as compared with the diabetic rats. The best results were observed in diabetic rats treated with ZnONPs in a dose of 10mg/kg b.w. with insulin. (figures 1, 2,3 and 4)**.**

4. Discussion

In the present study we evaluated the possible therapeutic effect of zinc oxide nanoparticles on streptozotocin-induced diabetic rats as well as its compared effect to insulin treatment.

Concerning to ZnONPs and glucose homeostasis, our results pointed out blood glucose levels were improved in diabetic rats with ZnONPs and/or insulin treatment . In the same line (Akaladi et al, 2014); (Umrani and Paknikar 2014) reported the ability of ZnONPs for improve the blood glucose in STZ-diabetic rats. Glucose is one of the body's main sources of energy. In normal physiology, the body maintains blood glucose levels within a narrow range (70-130mg/dl). The body regulates the processes that control the production and storage of glucose by secreting the endocrine hormone, insulin, from the pancreatic B-

cells. Insulin facilitates anabolic metabolism throughout the body .An increase in insulin above basal concentrations (2-12 mU/l) will decrease the release of glucose from the liver and increase glucose uptake into insulin-receptive tissues. This has the net effect of decreasing endogenous blood glucose appearance. (Pickup and Williams, 1997). Our results showed a great reduction in blood glucose level in diabetic groups treated with ZnONPs and insulin (76.1% and 80.2%) respectively. This showed a great antidiabetic activity of zinc oxide nanoparticles. as zinc has been elucidated to be a potent metal that improves glucose utilization and metabolism through its potent influence on enhancement of hepatic glycogenesis through actions on the insulin signaling pathway (Jansen et al., 2009). As well as (Umrani and Paknikar ,2014) reported that single administration of ZnONPs resulted in prominent glucose suppression during oral glucose tolerance test(OGGT), suggesting antidiabetic effects. Improved glucose tolerance in OGTT could be as a result of several possible mechanisms. Firstly, ZnONPs treatment might result in inhibition of intestinal a-glucosidase enzyme and thereby reduce glucose absorption. Secondly, blood glucose levels might be lowered as a result of increased glucose uptake in the liver and its subsequent storage (glycogenesis). Thirdly, enhanced glycolysis by ZnONPs could result in improved glucose disposal. Also, the antidiabetic effects of ZnONPs may be due to that zinc is closely involved in general metabolism of protein, carbohydrate, and lipids . In the case of glucose metabolism, zinc is a cofactor of key enzymes. It is an activator of fructose 1-6 diphosphate aldolase, and an inhibitor of fructose 1-6 diphosphatase (Faure et al., 1992). Also, our results showed a great reduction in blood glucose level in diabetic groups treated with ZnONPs and insulin after the second period, which was continued for a period of one month from the start of treatment compared to the first period and that was just two weeks after the start of treatment. These results matched with the results of the research made by(Umrani, and Paknikar , 2014) which reported that repeated administration of ZnONPs to diabetic rats showed better effects on

glucose intolerance compared with single-dose studies, suggesting improved efficacy after multiple dosing. Furthermore, suppression of glucose levels during OGTT was superior in Type 2 diabetic rats compared with Type 1 diabetic rats. This can be explained on the basis of the fact that b-cell mass in Type 1 diabetes is relatively lesser, which could result in limited glycolysis. Other data , have suggested that there is also a defect in zinc absorption associated with hyperglycemia or diabetes (Escobar et al., 1995). El-Yazigi et al.,(1993) evaluated both type 1 and Type 2 diabetes and found that zinc excretion were greater in diabetics than in matched controls and also found a positive correlation between zinc excretion and haemoglobin A1C concentration. Other research has been postulated that hyperglycaemia interferes with the active transport of zinc back into the renal tubular cells. In dogs, at least, experimentally-induced hyperglycaemia resulted in significant hyperzincuria (Kinlaw et al., 1983). In rats made diabetic by streptozotocin (STZ), who therefore do not have any genetic code for the metabolic defects seen in diabetes, increased zinc excretion has been routinely observed (Arthur, 1998). Even when the hyperglycaemia was reduced by the administration of insulin, hyperzincuria still persisted though on a reduced level (Failla and Gardil, 1985). ZnONPs treatment indicates inhibitory effects on glycogenolysis and gluconeogenesis, mechanisms that are active during the fasted state. Interestingly, zinc is reported to regulate glucagon secretion from pancreatic a-cells (Egefjord et al., 2010). As a result, glucagon-stimulated hepatic pathways (i.e., glycogenesis and gluconeogenesis) would be suppressed in the fasting state (Quesada et al., 2008) contributing to a reduction of fasted glucose levels.

Concerning to The increasing effect of ZnONPs on serum insulin level, Insulin is synthesized and stored in the secretory granules of the pancreatic p-cells, from where it is continually secreted into the pond circulation. Insulin secretion is controlled by multiple signals which include substrate availability, hormone

concentrations, and autonomice nervous system activity (Taylor et al., 1994). Extracellular glucose and amino acids are the principle regdators of insulin secretion (Pfeifer et al., 1981). In the early stages of DM-2, insulin is secreted in excess to compensate for high concentrations of circulating glucose (Defronzo, 1992). Over time, hyperinsulinemia may subside as pancreatic insulin responses to glucose diminish. The result is often a need for exogenous insulin administration to maintain normoglycemia (Taylor et al., 1 994). Our experiments revealed that ZnONPs could increase serum insulin level in diabetic groups treated with ZnONPs (79.4%) if compared with diabetic groups treated with insulin (97.3%). There are few studies that have investigated the therapeutic effect of ZnONPs on insulin levels or secretion. However, others have demonstrated that zinc could enhance the glucose stimulated insulin secretion from rat isolated pancreatic islets (Richards-Williams et al., 2008). Interestingly, on the basis of (Umrani and Paknikar, 2014), ZnONPs did not possess the risk of hypoglycemia in living organisms so it can act as an insulin secretagog. Also, increase serum insulin level in diabetic groups treated with ZnONPs this may be due to accumulation of zinc in the secretory vesicle of B cells using transporter 8 (Rungby, 2010). Zinc transporters are also identified in adipose tissues and liver (Mocchegiani et al., 2008). Such organs are the major regulator of glucose metabolism. Many studies, agree with our finding of a higher serurn insulin concentration in the zinc treated groups. (Quarterman et al., 1966) demonstrated that diet induced zinc deficiency in rats resulted in a decrease in the ability of the pancreas to secrete insulin in response to a glucose load. (Meyer and Spence , 2009), showed that decreased zinc in the pancreas may reduce the ability of the islet b-cells to produce and secrete insulin and zinc deficiency is positively correlated with diabetes and may also affect the progress of Type 2 diabetes (Chausmer ,1998).

Concerning to The effect of ZnONPs on lipid peroxidation (MDA) and nitric oxide (NO), our results pointed out that there is a significant increase in the levels of concentration of MDA and nitric oxide in the serum of diabetic rats, in contrast, was significantly reduced after treatment by ZnONPs. Zinc is a necessary factor in the variety of antioxidant enzymes e.g. Zn superoxide dismutase, Zn-metallothionein etc. (Arthur, 1998), other investigators have suggested that the Zn-metallothionein complex in the islets cells provides protection against free radicals produced in the cell from any cause. The more depleted the intracellular Zn stores, the less able the cell is to defend itself against this oxidative load. This provides a potential mechanism for zinc deficiency to affect the progress of diabetes mellitus. Gupta et. al., (1998) studied the lipid peroxides in the nervous system of rats fed a zinc deficient diet then they found that the peroxides increased in several regions of the brain and spinal cord while superoxide dismutase was reduced in cerebrum, cerebellum, hypothalamus, hypocampus, brainstem and spinal cord . (Aruoma, 1998) concluded that Copper and zinc, and manganese are indispensable metals for the activities of Cu,Zn-SOD and Mn-SOD, respectively. Therefore, dietary deficiencies of these minerals markedly decrease tissue Cu,Zn-SOD and Mn-SOD activities and result in peroxidative damage and mitochondrial dysfunction. Also , A deficiency of copper or zinc in rats also enhances cytochrome P-450 activity in microsomes of liver and lung, stimulates ROS generation, and increases intestinal iNOS expression (Wepnir, 2000) Such effects render the animal more susceptible to lipid peroxidation and gastrointestinal infection.

Conclusion

ZnONPs were elucidated as antidiabetic agents. They lead to induction of insulin synthesis and decreasing of blood glucose also has a depressant effects of lipids and protein oxidation.

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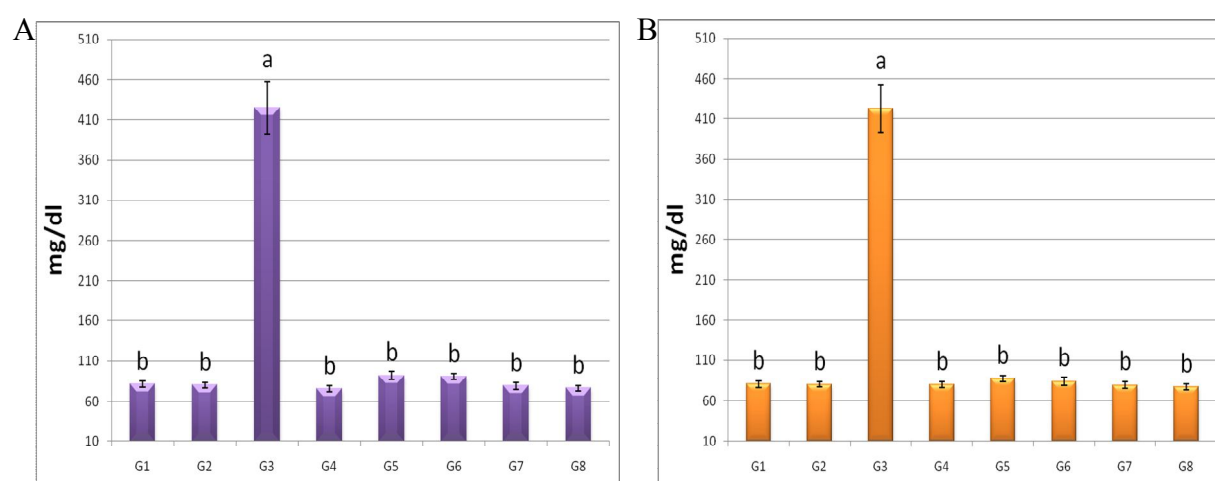
Figure 1. Blood glucose levels after 15 (A) and 30 (B) of ZnONPs and/or insulin treatment.

Column carrying different superscripts are significant at (**P** ≤0.001); G**1**, Control group; **G2**,Control positive group; **G3**,Diabetic group; **G4**, Diabetic group treated by insulin; **G5**,Diabetic group treated by ZnONPs (5 mg/kg); G**6**,Diabetic group treated by ZnONPs (10 mg/kg); **G7**, Diabetic group treated with ZnONPs (5mg/kg) &insulin; G**8**,Diabetic group treated with ZnONPs (10mg/kg) &insulin.
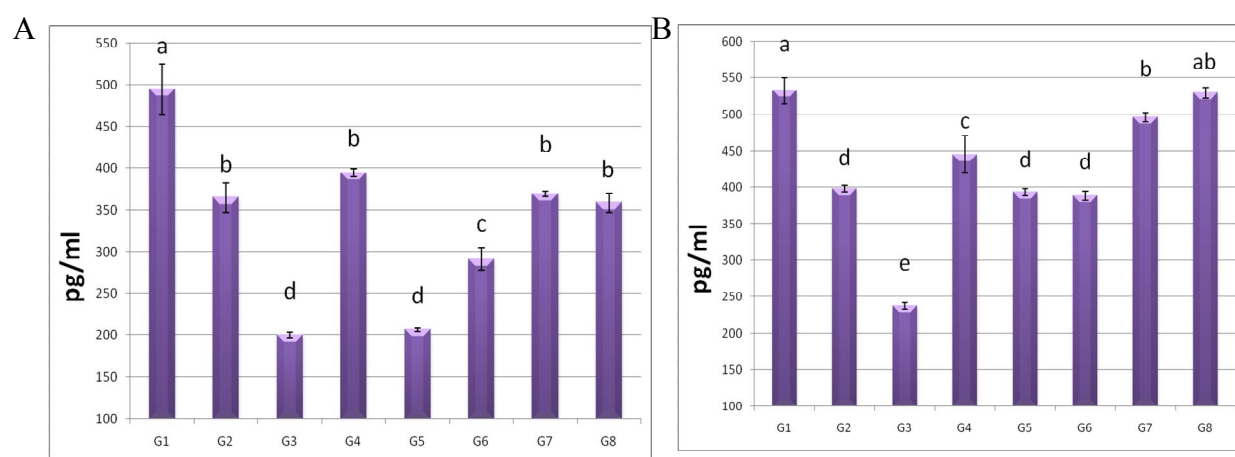

Figure 2. Serum insulin levels after 15 (A) and 30 (B) of ZnONPs and/or insulin treatment.

Column carrying different superscripts are significant at (**P** ≤0.001); G**1**, Control group; **G2**,Control positive group; **G3**,Diabetic group; **G4**, Diabetic group treated by insulin; **G5**,Diabetic group treated by ZnONPs (5 mg/kg); G**6**,Diabetic group treated by ZnONPs (10

mg/kg); **G7**, Diabetic group treated with ZnONPs (5mg/kg) &insulin; G8,Diabetic group treated with ZnONPs (10mg/kg) &insulin.
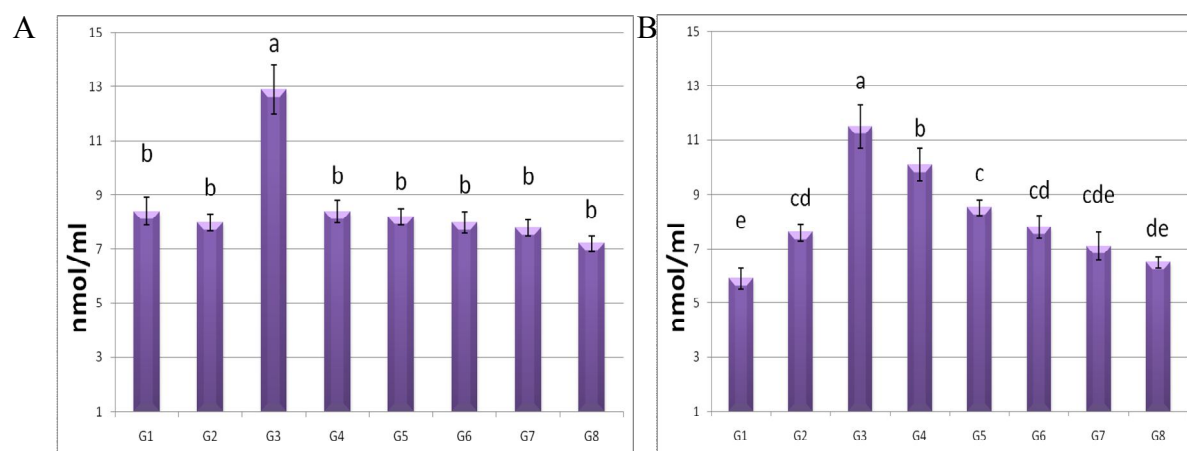

Figure 3. Serum malondialdehyd levels after 15 (A) and 30 (B) of ZnONPs and/or insulin treatment.

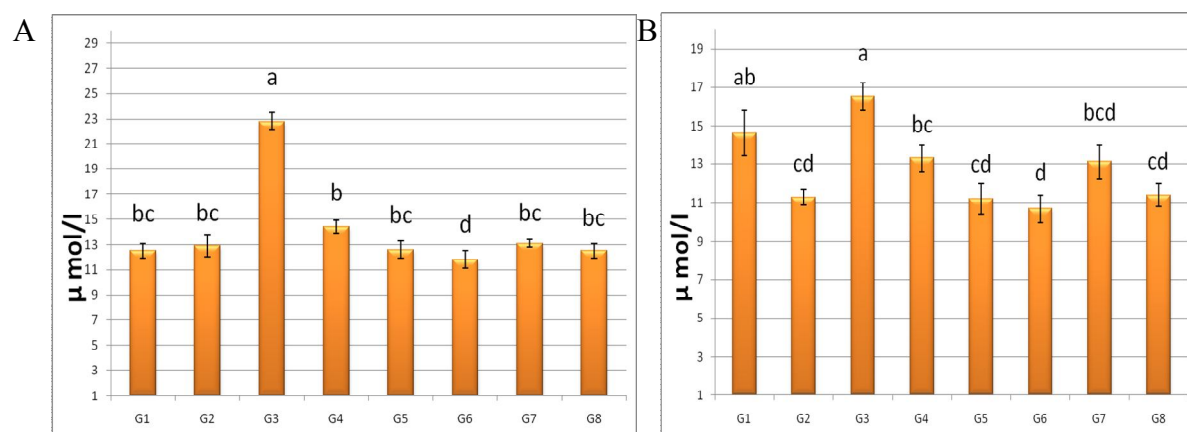Column carrying different superscripts are significant at ($P \leq 0.001$)

Figure 4. Serum nitric oxide levels after 15 (A) and 30 (B) of ZnONPs and/or insulin treatment.

Column carrying different superscripts are significant at ($P \leq 0.001$)

التأثيرالوقائى لجزيئات أكسيد الزنك النانونية على الأجهاد التأكسدى في الفئران المحدث بها البول السكري تجريبا

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الملخص العربي

ان أستخدام الجزيئات متناهية الصغر في الطب أصبح موضع اهتمام و جذب .وفي هذه الدراسة أستخدم الباحثين جزيئات أكسيد الزنك متناهية الصغر لتقييم مدي تأثيرها في مقاومة السكري.حيث استخدمت مائة وستين ذكرمن الجرذان البيضاء وزن ١٣٠ ± ٣٠ و عمر ١٦-١٢ أسابيع وتم تقسيمهم الي المجموعات الاتية :المجموعة الضابطة والتي لم تتناول أي عقار والمجموعة الضابطة ايجابيا والتي تم تجريعها عن طريق الفم ٥ملجم / كجم من محلول جزيئات أكسيد الزنك متناهية الصغر جرعة واحدة يوميا والمجموعة الفئران المصابة بالسكري و حقنت مادة الاستربتوزوتزسين مرة واحدة تحت الغشاء البريتوني (٥٠ ملغ / كلغ) ومجموعة السكري المعالجة بالانسولين والتي حقنت تحت الجلد ٢ وحدة دولية من الانسولين جرعة واحد يوميا ومجموعة السكري والمعالجة بجزيئات أكسيد الزنك متناهية الصغر بمعدل ٥ملجم/كجم جرعة واحدة فمويه يوميا ومجموعة السكري والمعالجة بجزيئات أكسيد الزنك متناهية الصغر بمعدل ١٠ملجم/كجم جرعة واحدة فمويه يوميا ومجموعة السكري المعالجة بكلا من الانسولين ٢وحدة دولية يوميا تحت الجلد وتطعم أيضا جرعة ٥ملجم/كجم من محلول أكسيد الزنك النانو فمويا جرعة واحدة يوميا ومجموعة السكري المعالجة بكلا من الانسولين ٢وحدة دولية يوميا تحت الجلد وتطعم أيضا جرعة ١٠ملجم/كجم من محلول أكسيد الزنك متناهية الصغر فمويا جرعة واحدة يوميا.ولقد برهنت النتائج انخفاض ملحوظ في مستويات جلوكوز الدم ومستويات النيتريك أكسيد و مستويات المالوندهيد وارتفاع كبير في مستويات هرمون الانسولين للفئران المعالجة بجزيئات أكسيد الزنك متناهية الصغر مع الانسولين في حين ظلت مستويات الجلوكوز والنيتريك أكسيد والمالوندهيد مرتفعة في الفئران المصابة بالسكري وأيضا أنخفضت مستويات الانسولين بالفئران المصابة بمرض السكري.

الخلاصة: تعمل جزيئات أكسيد الزنك متناهية الصغر كعلاج فعال لمقاومة مرض السكري من خلال خفض مستويات جلوكوز الدم وكذلك رفع مستويات الانسولين بالدم وتثبيط نشاط الشوارد الحرة الضارة.